REMARKS

Reconsideration of this application is requested. In order to address the items raised by the Examiner and to more particularly point out and distinctly claim that which the inventors consider to be their invention, claims 8-12, 14, 17-20 and 22-25 have been cancelled and replaced with new claims 26-38 which are derived from claims 8-12, 14, 17-20 and 22-25 as follows.

Claim 26

Claim 26 is derived from claim 8. The "emulsion" which was used in descriptor form relating to preconcentrate has been deleted from the term "**emulsion preconcentrate**" because of the confusion that its presence created. The words "**a dose of an anticancer drug**" have been deleted and replaced with "**a taxane**" which is a narrower and more specific term used in claim 12 (now cancelled) and found on page 1, line 7 and elsewhere in the specification. For clarification with respect to the taxane in the preconcentrate, the words "**dissolved in a carrier system composed of**" have been inserted; this phrase found in claim 2, now cancelled. The groups related to the hydrophobic component and to the hydrophilic component have each been converted to **Markush group format** by deleting the words "**at least one**" from each group, and instead inserting the phrase "**selected from the group consisting of**" at the beginning of each group, stating the individual members in singular number rather than plural number where applicable, adding the word "**a**" before each member of the group, following each member of the group with a comma, and replacing "**or mixtures thereof**" with "**and combinations thereof**" at the end of each group. The droplet size of "**2 to 10 microns**" has been deleted to reach agreement with the Examiner. The applicants revert instead to the words "**at most 10 microns**" originally used in claims 12 and 19. The term "**dose**" has been relocated to the final subsection at the end of claim 1 in the form of "**of a dose of said preconcentrate**." Reference to "**anticancer drug**" bioavailability has been replaced with the corrected antecedent "**taxane**" in the form of "**taxane bioavailability**."

The Boolean connector "**or**" relating to the final proviso has been replaced with the more restrictive Boolean connector "**and**," the proviso now requiring both formation of droplets in water of at most 10 microns and taxane bioavailability ranging from 25% to 60% of the taxane in a dose of the preconcentrate. Finally, the clarifying term "selected from the group consisting of water and simulated gastric fluid" found on page 7, Examples, 2nd paragraph and in cancelled claim 12, has been added to clarify the conditions under which droplets of at most 10 microns are formed.

Claim 27

Claim 27 is derived from claim 9 and depends on claim new claim 26. The term "emulsion" has been deleted as in claim 26.

Claim 28

Claim 28 is derived from claim 11 and depends on claim new claim 26. The term "emulsion" has been deleted as in claim 26.

Claim 29

Claim 29 is derived from claim 12. The term "**emulsion**" has been deleted from "**emulsion preconcentrate**" as in claim 26. The term "**a dose of**" has been deleted from "... **preconcentrate of a dose of at least one taxane**", reverting instead to "**preconcentrate of at least one taxane**." The groups related to the hydrophobic component and to the hydrophilic component have each been converted to **Markush group format** by deleting the words "**at least one**" from each group, and instead inserting the phrase "**selected from the group consisting of**" at the beginning of each group, stating the individual members in singular number rather than plural number where applicable, adding the word "**a**" before each member of the group as needed, following each member of the group with a comma, and replacing "**or mixtures thereof**" and "**or a mixture thereof**" with "**and combinations thereof**" at the end of each group. The droplet size of "**2 to 10 microns**" has been deleted in agreement with the Examiner. The applicants revert instead to the words "**at most 10 microns**" originally used in claims 12 and 19. The term "**dose**" has been relocated to the final subsection at the end of

claim 1 in the form of "of a dose of said preconcentrate." Reference to "**anticancer drug**" bioavailability has been replaced with the corrected antecedent "**taxane**" in the form of "**taxane bioavailability**." The Boolean connector "**or**" relating to the final proviso has been replaced with the more restrictive Boolean connector "**and**," the proviso now requiring both formation of droplets in water of at most 10 microns and taxane bioavailability ranging from 25% to 60% of the taxane in a dose of the preconcentrate. Correct reference is inserted as "**said at least one taxane**" as the antecedent related to taxane bioavailability. Finally, the clarifying term "selected from the group consisting of water and simulated gastric fluid" found on page 7, Examples, 2nd paragraph and in cancelled claim 12, has been added to clarify the conditions under which droplets of at most 10 microns are formed.

Claim 30
Claim 30 is derived from claim 14 and depends on claim new claim 29.

Claim 31
Claim 31 is derived from claim 17 and depends on claim new claim 29.

Claim 32
Claim 32 is derived from claim 18 and depends on claim new claim 29.

Claim 33
Claim 31 is derived from claim 22 and depends on claim new claim 29.

Claim 34
Claim 34 is derived from claim 23 and depends on claim new claim 29. The complete expression "**cytochrome P450**" found on page 5, line 18 has been used to clarify the otherwise potentially unclear term "**P450.**" P450 does not appear in any other form in the specification except associated with "cytochrome."

Claim 35
Claim 35 is derived from claim 24 and depends on claim new claim 34.

Claim 36

Claim 36 is derived from claim 25 and depends on claim new claim 29.

Claim 37

Claim 37 is derived from claim 19. As in claim 26, the relatively broader subject "**an anticancer drug**" has been replaced with the more limited "**a taxane**" from claim 12, from page 1, line 7, and from elsewhere. "Taxane " is a member of the class of anticancer drugs. The term "**emulsion**" has been deleted from "**emulsion preconcentrate**" as in claim 26. The term "**dose**" has been moved relative to its position in claim 19 to now precede rather than follow the words "**a storage-stable, self-emulsifying, non-aqueous, preconcentrate**," where these words are now followed by the phrase "of a taxane" that replaces "of ... an anticancer drug" as noted above. The groups related to the hydrophobic component and to the hydrophilic component have each been converted to **Markush group format** by deleting the words "**at least one**" from each group, and instead inserting the phrase "**selected from the group consisting of**" at the beginning of each group, stating the individual members in singular number rather than plural number where applicable, adding the word "**a**" before each member of the group as needed, following each member of the group with a comma, and replacing "**and mixtures thereof**" with "**and combinations thereof**" at the end of each group. The droplet size of "**2 to 10 microns**" has been deleted in agreement with the Examiner. The applicants revert instead to the words "**at most 10 microns**" originally used in claims 12 and 19. The Boolean connector "**or**" relating to the final proviso has been replaced with the more restrictive Boolean connector "**and**," the proviso now requiring both formation of droplets in water of at most 10 microns and taxane bioavailability ranging from 25% to 60% of the taxane in a dose of the preconcentrate. The clarifying term "selected from the group consisting of water and simulated gastric fluid" found on page 7, Examples, 2nd paragraph and in cancelled claim 12, has been added to clarify the conditions under which droplets of at most 10 microns are formed. Finally, the non-limiting term "comprising" has been replaced with the limiting term "consisting of" with respect to administering a dose of the preconcentrate of the current invention to eliminate the

possibility of using a combination of a taxane and a cyclosporine in the same formulation or by simultaneous administration.

Claim 38

Claim 38 is derived from claim 20 and depends on claim new claim 37. As in claim 26, the word "**emulsion**" has been deleted from "**emulsion preconcentrate**." The antecedent is no longer "**the anticancer drug**" because the latter has been deleted from claim 37. Rather, the antecedent is now "**the taxane**" of claim 37.

Favorable consideration of these new claims is requested.

Response to Lack of Enablement Rejection

With respect to items 2 and 3 in the Detailed Action, the Examiner has rejected claims 8-12, 14, 17-20 and 22-25 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, claims directed to formation of droplets having an average droplet size of 2 to 10 microns do not appear to be enabled. The applicants have addressed this issue by reverting to the use of the term "at most 10 microns" which is found in claims 12 and 19 in the application as filed and is described on page 3 in the Summary of the Invention (in the first paragraph) and on page 6 in the Detailed Description of the Invention (in the first and in the second paragraphs) in terms of "an average particle size in a range of about 10 nm to about 10 microns." On page 7 under the heading "Examples" in the second paragraph, an experiment is described to test the efficacy of forming microemulsions from the preconcentrates "by diluting the preconcentrate in 20-50 fold with water or simulated gastric fluid with gentle mixing or shaking. The aqueous medium temperature varied between 20 and 37°C. Particle size analysis was then carried out using a photon correlation spectroscopy based particle sizer, Nicomp 370." Data are reported thereafter in examples correspond to volume weighted particle size. Furthermore, the term "preconcentrate" rather than the term "emulsion

preconcentrate" is now employed in claims 26, 27, 28, 29, 37, and 38 which are each derived from cancelled claims as described above.

The examiner notes in point 3 of the Detailed Action that eight factors (a) through (h) are to be considered in a determination of "undue experimentation" in the system as claimed. In response to this rejection, applicants have reverted to the term "at most 10 microns" and have inserted into the claims the expression "said preconcentrate, when mixed with an aqueous medium selected from the group consisting of water and simulated gastric fluid" that is found in the specification on page 7, Examples, 2nd paragraph to clarify the conditions under which droplets of at most 10 microns are formed. Furthermore, the re is no mention in the active claims of the formation of emulsions in the gastrointestinal tract. In view of these changes in the claims, the need for perceived undue experimentation is obviated. As noted above, the specification provides specific guidance with respect to determination of particle size under a limited selection of conditions. A skilled artisan would routinely follow the examples described in the specification to determine particle size.

Response to Art-Based Rejection

With respect to items 4 and 5 in the Detailed Action, the Examiner has rejected claims 8-12, 14, 17-20 and 22-25 under 35 U.S.C. 103(a) as being unpatentable over Hauer et al (US 5,342,625) in view of Shively (US 5,407,683). To the extent the examiner may regard this art relevant to the new claims, the rejection is traversed. Hauer et al. in US Patent 5,342,625 disclose "pharmaceutical compositions comprising a cyclosporin, e.g. Ciclosporin, ... in "microemulsion pre-concentrate" and microemulsion form (see '625, Abstract).

Hauer et al. note that microemulsions in general were well known at the time of their invention (see three paragraphs in '625 at column 5, line 58 to column 6, line 24):

> (i) "The term microemulsion as used herein is used in its conventionally accepted sense as a non-opaque or substantially non-opaque colloidal dispersion comprising water and organic components including hydrophobic (lipophilic) organic components. Microemulsions are identifiable as possessing one or more of the

following characteristics. They are formed spontaneously or substantially spontaneously when their components are brought into contact, that is without substantial energy supply, e.g. in the absence of heating or the use of high shear equipment or other substantial agitation. They exhibit thermodynamic stability. They are monophasic. They are substantially non-opaque, i.e. are transparent or opalescent when viewed by optical microscopic means. In their undisturbed state they are optically isotropic, though an anisotropic structure may be observable using e.g. x-ray technique."

(ii) "Microemulsions comprise a dispersed or particulate (droplet) phase, the particles of which are of a size less than 2,000 A, hence their optical transparency. The particles of a microemulsion may be spherical, though other structures are feasible, e.g. liquid crystals with lamellar, hexagonal or isotropic symmetries. Generally, micro-emulsions comprise droplets or particles having a maximum dimension (e.g. diameter) of less than 1,500 A, e.g. typically from 100 to 1,000 A."

(iii) "(For further discussion of the characteristics of microemulsions see, e.g. Rosof, Progress in Surface and Membrane Science, 12, 405 et seq. Academic Press (1975); Friberg, Dispersion Science and Technology, 6 (3), 317 et seq. (1985); and Muller et al. Pharm. Ind., 50 (3), 370 et seq. (1988))."

Hauer et al. refer to cyclosporins as:

"... a class of structurally distinctive, cyclic, poly-N-methylated endecapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity" (see column 1, lines 11-15).

Hauer et al. does not recite that cyclosporins are antitumor agents. Rather, Hauer et al. recites that cyclosporin exhibits activity in "... reversing tumor resistance to cytostatic therapy ... (see column 3, lines 16-21) and acts "... as an agent for reversing or abrogating anti-neoplastic agent resistance in tumours" (see column 2, lines 15-18).

Hauer et al. does not refer to taxanes nor does it disclose formulations of taxanes.

In contrast to cyclosporins, which act only as adjuvants for potentially reversing antineoplastic agent resistance in tumors, and which are not considered to be antineoplastic or cytotoxic agents, the taxanes such as paclitaxel were known prior to the disclosure of Hauer et al to be cytotoxic antineoplastic agents and to act with anti-mitotic activity. Paclitaxel, and taxanes in general, bind and stabilize microtubules and thereby inhibit cell division; for example, see US Patent 5,380,751, column 1, lines 37-43 that recites:

> "Paclitaxel is unique among antimitotic drugs in that it promotes the assembly of stable microtubules from tubulin even under otherwise unfavorable conditions. The drug binds to microtubules, stabilizing them from depolymerization, thus disrupting the tubulin-microtubule equilibrium and consequently inhibiting mitosis. The mechanism of action, toxicology, clinical efficacy, etc. of paclitaxel are reviewed in a number of articles, such as in the article by Rowinsky et al. in Taxol: A Novel Investigational Antimicrotubule Agent, J. Natl. Cancer Inst., 82: pp 1247-1259 (1990)."

Chemically and molecularly, cyclosporines and taxanes are very different. There is no suggestion in Hauer et al. that the compositions and methods disclosed in Hauer et al. will find application in with molecules other than cyclcosporins, a class of molecules quite different from and dissimilar to the taxane class of molecules. Cyclosporine is representative of the class of cyclosporines. It a cyclic peptide of 11 amino acids (see for example Bollinger et al, US Patent 4,384,996 "Novel cyclosporins") and contains amide bonds in the ring system, while taxanes such as paclitaxel are carbocyclic diterpenoids (see for example Colin et al., US Patent 4,814,470, "Taxol derivatives, their preparation and pharmaceutical compositions containing them").

A comparison of properties between cyclosporin and paclitaxel is provided below in the format of "Property = Cyclosporine vs. Paclitaxel," respectively to compare, for example, Melting point = 150° C vs. 213° C (decomp); Empirical formula = $C_{62}H_{111}N_{11}O_{12}$ vs. $C_{47}H_{51}NO_{14}$; Molecular weight = 1,203 Dalton vs. 854 Dalton; and Solubility in methanol = Freely soluble vs. Crystallized from methanol.

Differences in chemical structure between peptide-like cyclosporins and hydrocarbon-based taxanes are obvious to one skilled in the art. In the cyclic oligopeptide cyclosporine the macrocyclic ring is composed entirely of amino acid-derived amide bonds, and formulation expertise relevant to peptides and proteins, which are molecules containing similar amino acid-derived peptide bonds, is logically most immediately relevant to cyclosporines to one skilled in the art. However, in the carbocyclic taxane system, the backbone of the ring structure is composed of carbon-carbon bonds, and formulation expertise relevant to carbocyclic hydrocarbon systems, which are composed of carbon-carbon bonds, is logically most immediately relevant to taxanes to one skilled in the art. As the Examiner knows, the multiple peptide amide groups found in the cyclosporine ring system are relatively polar functional groups because of the presence of amide carbonyl oxygen atoms and amide nitrogen atoms which are more electronegative than carbon atoms and which tend to be more electron-rich relative to carbon when bonded to carbon as they are in amide bonds. Amide groups, because they contain relatively electron-rich carbonyl oxygen and nitrogen atoms, are well known to participate in both intramolecular and intermolecular interactions as a result of phenomena such as dipole-dipole interactions leading to restrictions in degrees of freedom in the cyclosporine ring configurations both in solution and in the solid state. Amide carbonyl oxygen and amide nitrogen groups such as those found in cyclosporins are well known to be capable of hydrogen bonding with polar proton donors such as water in aqueous media and with hydroxyl-containing molecules such as alcohols and carboxylic acids. On the other hand, the relatively non-polar carbon-carbon bonds in carbocyclic taxane molecules, unlike the array of heteroatoms in the cyclic oligopeptide amide bonds of cyclosporines, are known not to form strong associations with polar molecules and are known not to form hydrogen bonds with polar proton donors such as water in aqueous media and with hydroxyl-containing molecules such as alcohols and carboxylic acids. In spite of the ability to form hydrogen bonds with water, cyclosporins are poorly water-soluble because the intramolecular and intermolecular forces provide a lower energy configuration in the solid state than can be overcome by the energy

provided by hydrogen bonding with water in a solution state. On the other hand, taxanes are poorly water-soluble because the large numbers of carbon-carbon non-polar bonds are not able to interact with water through hydrogen bond formation or to polarize adequately enough to induce association with polar solvents such as water. One skilled in the art would look away from the teachings of Hauer et al. when considering compositions and methods to formulate taxanes.

In addition, when one skilled in the art considers formulations on a molecular level, the potential associations among molecules of hydrophobic, hydrophilic, surfactant, and cyclosporine components in a cyclosporine-containing composition of Hauer et al. has to be quite different from the associations among molecules of hydrophobic, hydrophilic, surfactant, and taxane components in a self-emulsifying, non-aqueous, preconcentrate of a taxane of the current invention. One skilled in the art would expect that at the interface between molecules of a cyclosporin, which contains polarized amide carbonyl-oxygen and amide nitrogen heteroatoms in the ring structure, and a mixture of components in the composition, one would find a predominance of polarizable molecules capable of dipole-dipole interactions with cyclosporine. Such molecules will contain heteroatoms and/or be capable of hydrogen-bonding with amide heteratoms in the cyclosporins. The portions of these molecules that associate with cyclosporine amide bonds are hydrophilic, i.e., they associate with and prefer water for the same reasons they associate with amide bonds in cyclcosporin. Thus, one would expect the cyclosporin molecules to associate with polarizable hydrophilic molecules and with hydrophilic portions of surfactant molecules. On the other hand, relatively the non-polar carbocyclic ring-containing taxanes are expected to associate preferentially with relatively non-polar molecules such a hydrophobic components in the preconcentrate and with relatively non-polar portions of surfactant molecules. As the distance increases from the amide-bond-containing cyclosporine molecules in the compositions of Hauer et al., and as the distance increases from the carbocyclic-bond-containing taxane molecules in the compositions of the current invention, different relative molecular interactions and molecular orientations are expected, induced by and as a result of the inherently different molecular orientations

present at the respective cyclosporine and taxane molecules. Thus, the relative molecular structures and associations in the amide-containing cyclosporine compositions are different from the relative molecular structures and associations in the carbocyclic-bond-containing taxane compositions.

Because of the differences between these two classes of unrelated molecules, it would not be obvious to one skilled in the art to formulate taxanes such as paclitaxel according to Hauer et al's teaching for cyclosporins. Indeed, Shively (US 5,407,683) does not allude at all to microemulsion technology or to cyclosporine compositions of Hauer et al. (US 5,342,625). The relatively large difference in the melting points of cyclosporin and paclitaxel suggest differences in their crystal lattice are to be expected, and therefore differences in their interaction with and affinities for various hydrophilic and lipophilic solvents are to be expected. Approaches that a person skilled in the art would take to form a microemulsion that contains a member of one of the cyclosporin class of compounds are therefore expected to be different from formulation approaches that a person skilled in the art would take to make a microemulsion containing a member of the taxane class of compounds. Only with the benefit of hindsight and the disclosure of the current application would a person skilled in the art (such as Shively) attempt to replace cyclosporine with a taxane in the compositions of Hauer et al.

The use of a combination of a taxane and a cyclosporine composition of Hauer et al. in an effort to reduce the growth of a tumor is not a subject of the current claims. Taxanes are structurally different from cyclosporins, have different mechanisms of action in the treatment of cancer, and interact in a different fashion with the components of a preconcentrate such as provided in the current application.

The above discussion is reinforced by the consideration of M.C. Martini in "Interet des vehicules microemulsionnes" Chapter 16, p. 412-440 in Formes Pharmaceutiques pour Application Locale, Edited by M. Seiller and M-C Martini, Tec Doc Publishers, Paris (1996) who writes on pages 412-417 about formulations of microemulsions: "The formulation of pharmaceutical microemulsions is fastidious since it is always dependent on subtle characteristics of the raw materials, which are often not present in regulated

Pharmacopeia. It is equally dependent on the physico-chemical characteristics of the active principal ingredients that have to be incorporated [in the microemulsions]."

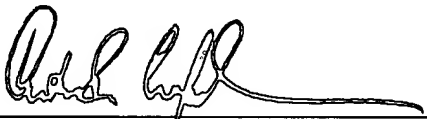
Response to Item 6 of the Detailed Action

The revised new claims do not contain reference to formation of droplets of any size in the GI tract. The confusing reference to "emulsion" in "emulsion preconcentrate" has been elimination from the claim language. As described above, the compositions of cyclosporins in Hauer et al. ('625) are different from the compositions of the current invention. There is no evidence or teaching in Hauer or in Shively that range of bioavailability of a cyclosporin in a composition of Hauer et al. should be related to the range of bioavailability of a taxane in a composition of the current invention. That such ranges are similar can only be held to be coincidental in view of the previous analysis. The applicants believe that the new claims distinctly claim the current invention in a manner that distinguishes the current invention from that of Hauer et al.

Reconsideration and favorable action are solicited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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